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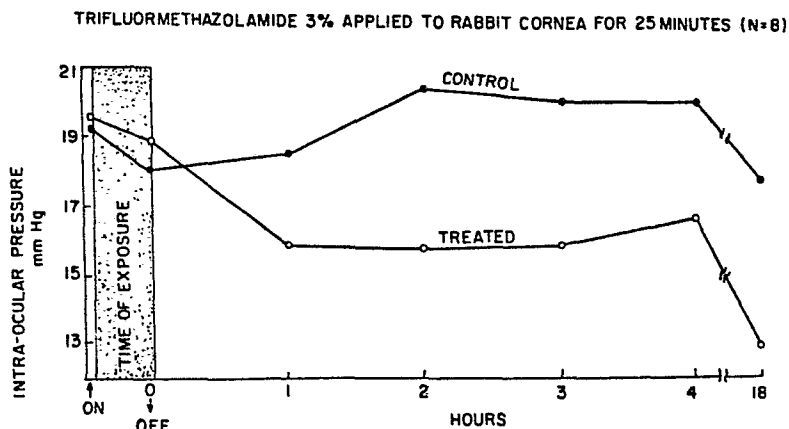
(54) Method and composition for reducing intraocular pressure.

(57) Method and composition for reducing intraocular pressure and reducing aqueous humor formation by applying topically to the cornea an effective amount of an aqueous solution of a carbonic anhydrase inhibitor comprising a sulfonamide having the following properties:

- a. sufficiently soluble in water to form a 1-5%, by weight, solution or a pKa of not greater than 7.0;
- b. ether partition coefficient of at least 1.0;

- c. chloroform partition coefficient of at least 0.01;
- d. dissociation constant against carbonic anhydrase of not more than 3×10^{-8} molar;
- e. first order rate constant for penetration of the sulfonamide through a isolated rabbit cornea of at least 0.002 hr.^{-1} ;
- f. not injurious to the cornea; and
- g. stable in aqueous solution and in contact with the cornea.

FIG. 1.



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METHOD AND COMPOSITION FOR REDUCING INTRAOCULAR
PRESSURE

TECHNICAL FIELD

This invention is directed to a process and composition for reducing intraocular pressure and reducing aqueous humor formation by applying topically to the cornea an effective amount of an aqueous solution of a carbonic anhydrase inhibitor.

BACKGROUND OF THE INVENTION

Glaucoma is well known as a condition in which the internal pressure in the eye increases to the extent that it causes damage to the optic nerve and may eventually cause blindness. This condition is primarily caused by the failure of aqueous humor to properly drain from the eye, resulting in a high internal or intraocular pressure. It has been recognized that the formation of aqueous humor is the result of the activity of the enzyme carbonic anhydrase which is employed by the human body to reversibly catalyze the hydration of carbon dioxide. Compounds, principally heterocyclic sulfonamides, are known which inhibit the activity of carbonic anhydrase and thus control the production of aqueous humor and the intraocular pressure resulting therefrom. [Havener, Ocular Pharmacology, 4th Ed. (1978, C.V. Moseby); Maren, Investigative Ophthalmology, Vol. 13, pp 479-484 (1974); Becker, Am. J. of Ophthalmology, 39, 177 (1955)].

It is necessary to administer these materials

parenterally in order to achieve intraocular pressure reduction. Parenteral administration requires relatively large dosages and very often results in the patient experiencing fatigue, depression, anorexia, numbness and
5 tingling sensations.

It has now been discovered that certain carbonic anhydrase inhibitors can be administered topically, i.e., applied directly to the cornea, and that these compounds will penetrate the cornea and be immediately effective in
10 inhibiting the activity of carbonic anhydrase and decreasing intraocular pressure and aqueous humor flow resulting from this activity.

The topical or local applicability of intraocular pressure depressants offers several major
15 advantages over drugs requiring parenteral administration. Topical applicability avoids the unpleasant side effects described above which result from systemic applications of carbonic anhydrase inhibitors. In addition, topical application enables a more rapid, localized concentration
20 of the drug at the situs requiring the drug's action.

BRIEF SUMMARY OF THE INVENTION

This invention provides a method and composition particularly adapted for reducing intraocular pressure and reducing aqueous humor formation. It has been discovered
25 that the topical application to the cornea of certain anhydrase inhibitors effects a reduction of aqueous humor formation and intraocular pressure. These carbonic anhydrase inhibitors comprise pharmaceutically acceptable sulfonamides having the following properties:

- 30 a. sufficiently soluble in water to form a 1-5%,
by weight, solution or pKa of not greater than 7.0;
 b. ether partition coefficient of at least 1.0;
 c. chloroform partition coefficient of at least
0.01;

d. dissociation constant against carbonic anhydrase of not more than 3×10^{-8} molar;

e. first order rate constant for penetration of said sulfonamide through an isolated rabbit cornea of at least 0.0002 hr^{-1} .

f. not injurious to the cornea; and

g. stable in solution and in contact with the cornea.

DETAILED DESCRIPTION OF THE INVENTION

10 In accordance with the invention it has been found that certain carbonic anhydrase inhibitors can be safely and advantageously applied directly to the cornea in the form of drops of aqueous solution. These inhibitors must have certain properties in order to
15 effectively function in this fashion. First, the inhibitor in its acid form must have a pKa which is not greater than 7.0, or the inhibitor in the acid form must be sufficiently soluble in water to produce a 1-5% solution. This property is important in that it permits
20 the compound to be used in an 1-5% aqueous solution at a pH below 8 and therefore can be applied to the eye at a relatively neutral pH. The pKa may be measured by titrating the compound with NaOH and finding the point at which half of the compound is neutralized. The pH at this
25 point is the pKa.

Another necessary property of these compounds is that they must possess an ether partition coefficient of at least 1.0. This property in conjunction with the chloroform coefficient is a measure of the lipid
30 solubility of this compound. This is a critical feature since the compound must be readily absorbed by the lipid materials in the eye and be available for intimate contact with carbonic anhydrase so as to control its activity. This property is measured by preparing an aqueous solution

of the compound at pH7 and shaking the solution with an equal volume of ether until equilibrium is achieved in the system. An ether layer and an aqueous layer are formed, separated, and each analyzed for its content of the compound. The coefficient is the ratio of the amount of the compound in the ether layer to the amount of the compound in the aqueous layer. See, e.g., Maren, J., Pharm. Expt. Therap. 130, p 26, (1960) for the method of analysis for the compound in each layer.

Another critical property necessary in the inhibitors employed in this invention is the chloroform partition coefficient which must be at least 0.01. This property also relates to the lipid solubility of the compound employed and it is measured as described above with respect to ether. The procedure is the same as that described above except that chloroform is employed in place of ether.

Another necessary property in the inhibitors employed in this invention is that they must have a dissociation constant against carbonic anhydrase of not more than 3×10^{-8} molar. This property denotes that the compound has high activity against carbonic anhydrase in the ciliary process of the eye which is, at least in part, responsible for the secretion of aqueous humor. The dissociation constant is the concentration of the compound that will inhibit one-half of the carbonic anhydrase in a test system wherein the conditions are so arranged that the compound is present in excess of the carbonic anhydrase. The test system is described in Maren, supra, and in a subsequent article by Maren in the same volume at page 389.

Still another critical property of the inhibitor compounds employed in this invention is that the compound must have a first order rate constant for penetration of the compound through the isolated cornea of a rabbit of at

least 0.000 hr^{-1} . This property is important in that it sets a standard for a speed in which the inhibitor will pass through the cornea to the interior of the eye and be available to inhibit the activity of carbonic anhydrase in that location. This rate constant is measured by employing a cornea which has been excised from an animal and mounted in a laboratory apparatus in such a way that two different aqueous solutions are separated from each other by that cornea and analysis can be made of the solution at timed intervals so as to determine the rate at which the dissolved compound in one solution appears in the second solution. Analysis of the solutions may be made by the method of the Maren articles cited above. The permeability system employing an animal cornea is described in Hull et al, Invest. Ophthalm. 13, p 457, 1974.

Still another critical property of the compounds employed in this invention is that they be pharmaceutically acceptable and not be injurious to the cornea being treated.

The final property which is necessary for a compound used in this invention is that it be stable against decomposition in solution and in contact with the cornea. This property may be tested by dissolving the compound in aqueous solution and in solution containing corneal tissue to determine whether the compound has remained stable or has decomposed into other materials.

None of the carbonic anhydrase inhibitors previously employed by parenteral administration is useful in the process of this invention because they do not meet all of the criteria mentioned above and therefore cannot be used topically. Perhaps the best known inhibitor in the prior art is acetazolamide (2-acetylamino-1,3,4-thiadiazole-5-Sulfonamide) which cannot be made into a water solution below pH8 at concentration greater than

0.05%. The pKa is 7.4; the ether partition coefficient is 0.14 and the chloroform coefficient is 0.001. This material has been tried and found to be completely unsuitable in lowering intraocular pressure by topical administration. [Foss, Am. J. Ophthalmology, 39, 336 (1955)]. Methazolamide (2-acetylmino-3-methyl- Δ^2 -1,3,4-thiadiazoline-5-Sulfonamide) is another known carbonic anhydrase inhibitor but it is unsuitable in the process of this invention. This compound has a pKa of 7.4 and cannot be made into a neutral solution with a concentration of more than about 0.2%. In a series of tests the intraocular pressure was not reduced and the production of aqueous humor was not reduced except to a very slight extent in one of the series of tests. Still another prior art inhibitor is ethoxzolamide (6-ethoxy-benzothiazole-2-sulfonamide) having properties somewhat similar to those of methazolamide. This material has a pKa of 8.1 and cannot be made into an aqueous solution at a concentration above about 0.004%. This drug is ineffective in topically treating the eye to reduce intraocular pressure.

An inhibitor which is useful in this invention is 2-bromoacetylmino-1,3,4-thiadiazole-5-sulfonamide, commonly named bromacetazolamide. This compound has a pKa of 5.7; an ether partition coefficient of 2.0; a chloroform partition coefficient of 0.01; a dissociation constant of 10^{-8} molar; a rabbit cornea penetration rate constant of 0.0003 hr.^{-1} ; it produces no injury or clouding in the cornea upon being applied in a 2-5% solution; and it is stable in solution for at least several weeks. The preferred concentration in which this drug may be applied to the eye is 1-5%, the actual choice being dependent upon several factors such as, the severity of the disease and individual patient variations.

Another compound which is useful in the process of this invention is 2-trifluoroacetylmino-3-methyl- Δ^2 -1,3,4-thiadiazoline-5-sulfonamide, its common name being trifluormethazolamide. This compound meets all of the qualifications as set forth for the process of this invention, although it is not as stable in solution as bromacetazolamide. This compound has a pKa of 6.4; an ether partition coefficient of 6.0; a chloroform partition coefficient of 0.3; a dissociation constant of 3×10^{-8} molar; a rabbit cornea penetration rate constant of 0.003 hr.^{-1} ; it does not injure or cloud the cornea in a 2-5% solution; and is stable in solution for two hours.

Still another compound useful in this invention is 2-trichloroacetylaimino-3-methyl- Δ^2 -1,3,4-thiadiazoline-5-sulfonamide, its common name being trichlormethazolamide. It has a pKa of 6.8; an ether partition coefficient of 21, a chloroform partition coefficient of 3.0; a dissociation constant of 2×10^{-8} molar; a rabbit cornea penetration rate constant of greater than 0.001 hr.^{-1} ; it does not injure or cloud the cornea in 2-5% solution; and it is stable in solution for at least six hours.

All three of the above-described compounds, i.e., bromacetazolamide, trifluormethazolamide, and trichlormethazolamide as well as other compounds meeting the above-listed criteria are useful and operable in lowering intraocular pressure and in reducing the formation of aqueous humor by topical treatment of the eye in accordance with this invention.

Sulfonamides which are sufficiently soluble in water to form 1-5%, by weight, solution may be utilized in the acid form. Those sulfonamides that are not sufficiently water soluble are utilized in the form of their pharmaceutically acceptable water-soluble salts, i.e., sodium, potassium, triethanolamine, etc. The

sulfonamide solutions are applied topically to the eye by exposing the entire cornea to the solution for a time sufficient for penetration into the eye of an amount of carbonic anhydrase inhibitor sufficient to
5 effect a reduction in aqueous humor formation and intraocular pressure. Generally, when employing solutions containing 1-5% by weight of sulfonamide, exposure to the cornea for from about 10 to 30 minutes is adequate to enable an effective penetration of sulfonamide. The exact
10 time of exposure will vary depending on the nature of the sulfonamide.

Figs. 1-3 demonstrate the effect on the intraocular pressure in the eye of rabbits exposed to solutions of sulfonamides according to the invention. The
15 shaded portions of the figures indicate the times of exposure of the eye to the active solutions. The other eye of the rabbit is used as a control. Intraocular pressure is measured utilizing the pneumotonograph according to the method of Quigly et al (Amer. J. Ophthal.
20 80, p. 266 (1975)). Briefly, an electronically controlled probe is gently placed on the cornea. The probe consists of a membrane, piston, and gas chamber arranged so that the eye pressure is translated electronically to a scribe on moving graph paper which records the pressure.

25 The volume and flow of aqueous humor is measured according to the methods of Oppelt, Invest. Ophthal., Vol. 6, p. 76 (1967).

While the invention has been described with respect to certain specific embodiments, it will be
30 appreciated that many modifications and changes may be made by those skilled in the art without departing from the spirit of the invention. It is intended, therefore, by the appended claims to cover all such modifications and changes as fall within the true spirit and scope of the
35 invention.

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CLAIMS

1. A method of reducing aqueous humor formation and intraocular pressure comprising topically applying to the cornea an amount of an aqueous solution of a carbonic anhydrase inhibitor and for a time sufficient to effect a reduction of aqueous humor formation and intraocular pressure, said carbonic anhydrase inhibitor comprising a pharmaceutically acceptable sulfonamide having the following properties:
 - a) sufficiently water soluble to form a 1-5%, by weight, solution or pK_a of not greater than 7.0;
 - b) ether partition coefficient of at least 1.0;
 - c) chloroform partition coefficient of at least 0.01;
 - d) dissociation constant against carbonic anhydrase of not more than 3×10^{-8} molar;
 - e) first order rate constant for penetration of said sulfonamide through a rabbit cornea of at least 0.002 hr.^{-1} ;
 - f) not injurious to the cornea; and
 - g) stable in solution and in contact with the cornea.
2. A composition adapted for topical application to the eye in unit dosage form comprising an aqueous solution of an amount of carbonic anhydrase inhibitor sufficient to reduce aqueous humor formation and to reduce intraocular pressure, said carbonic anhydrase inhibitor comprising a pharmaceutically acceptable sulfonamide having the following properties:

- 2 -

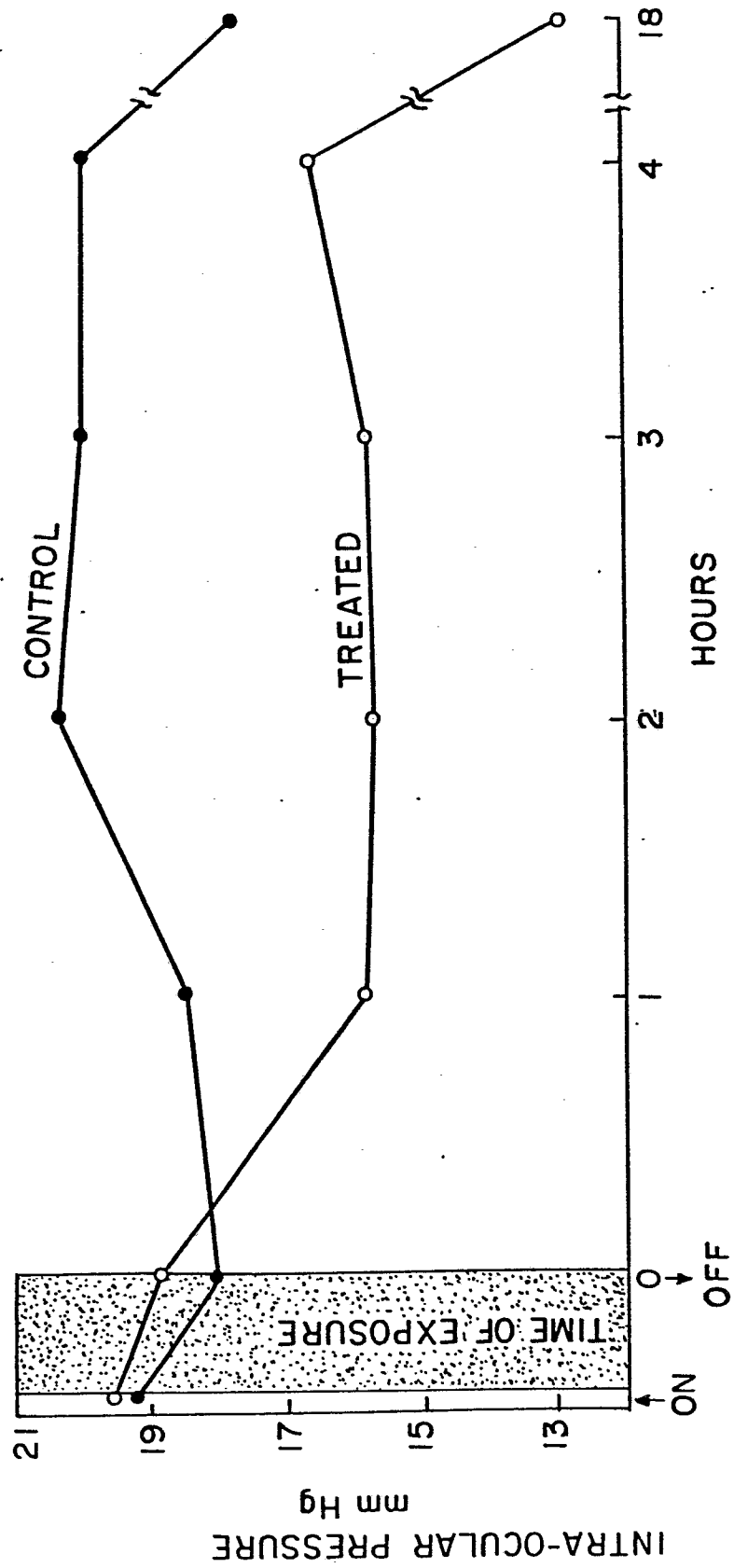
- a) sufficiently soluble in water to form a 1-5%,
by weight, solution or a pKa of not greater than 7.0;
b) ether partition coefficient of at least 1.0;
c) chloroform partition coefficient of at least
5 0.01;
d) dissociation constant against carbonic
anhydrase of not more than 3×10^{-8} molar;
e) first order rate constant for penetration of
said sulfonamide through a rabbit cornea of at least
10 0.002 hr.^{-1} ;
f) not injurious to the cornea; and
g) stable in solution and in contact with the
cornea.
3. The invention according to claim 1 or 2 wherein
15 said aqueous solution contains 1-5% by weight of said
carbonic anhydrase inhibitor.
4. The invention according to claim 1, 2 or 3 wherein
said sulfonamide is a heterocyclic sulfonamide.
5. The invention according to claim 4 wherein said
20 sulfonamide is a thiadiazoline sulfonamide.
6. The invention according to claim 4 wherein said
sulfonamide is 2-bromoacetylamino-1,3,4-thiadiazole-5-
sulfonamide.
7. The invention according to claim 5 wherein said
25 sulfonamide is 2-trifluoroacetylmino-3-methyl- Δ^2 -
1,3,4-thiadiazoline-5-sulfonamide.
8. The invention according to claim 5 wherein said
sulfonamide is 2-trichloroacetylmino-3-methyl- Δ^2 -
1,2,4-thiadiazoline-5-sulfonamide.

9. The compound 2-trifluoro-acetylimino-3-methyl- Δ^2 -1,3,4-thiadiazoline-5-sulfonamide.
10. The compound 2-trichloroacetylimino-3-methyl- Δ^2 -1,3,4-thiadiazoline-5-sulfonamide.

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FIG. 1.

TRIFLUORMETHAZOLAMIDE 3% APPLIED TO RABBIT CORNEA FOR 25 MINUTES (N=8)



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FIG. 2.

BROMACE TAZOLAMIDE 5% APPLIED TO RABBIT CORNEA FOR 1 HOUR

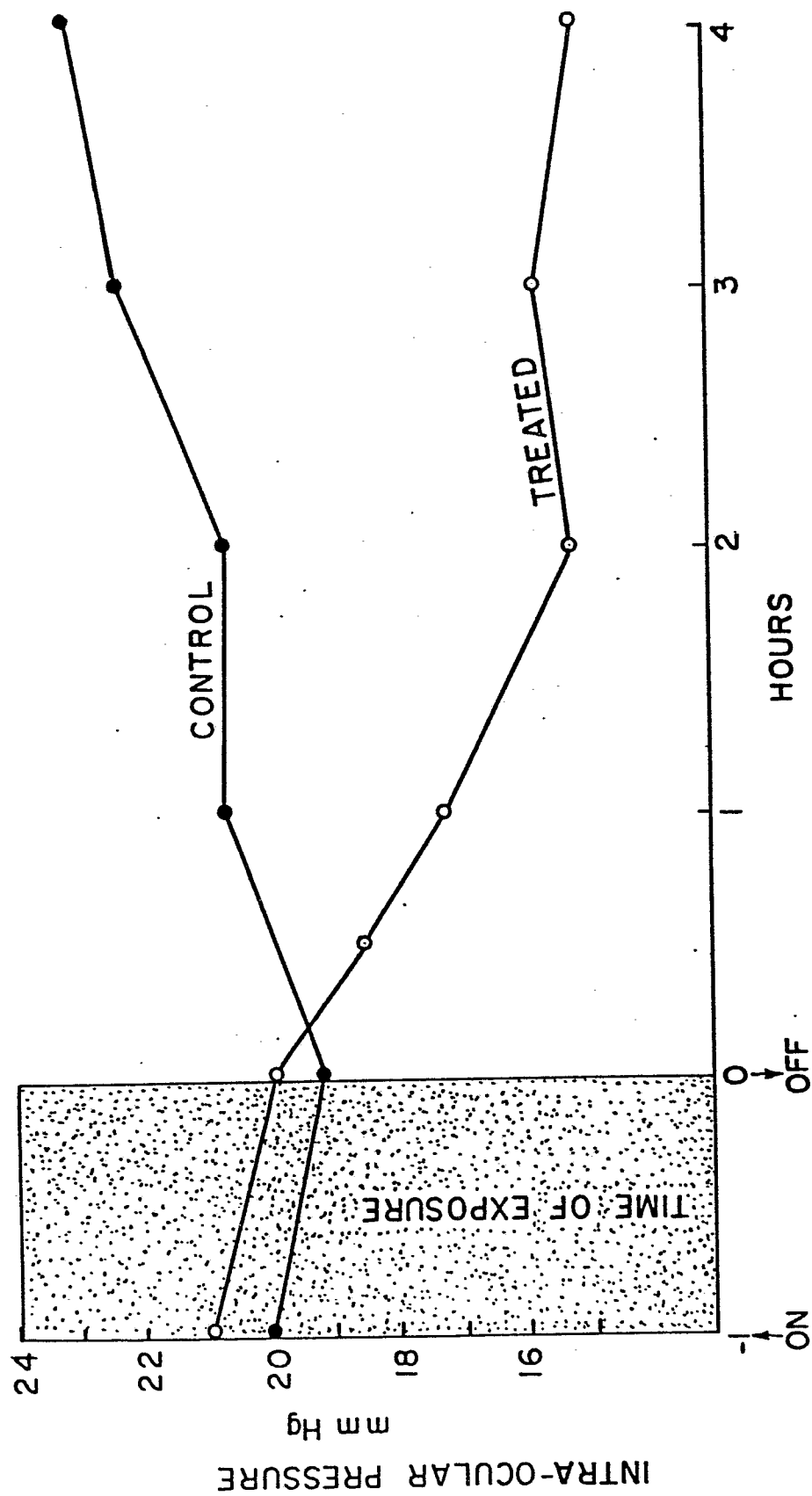


FIG. 3.

Δ INTRA-OCULAR PRESSURE IN RABBITS ($n=5-7$) FOLLOWING
10' CORNEAL APPLICATION OF 1.2% (35mM) TRICHLOROMETHAZOLAMIDE

